IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	SIEGEL, Steven	Examiner:	TCHERKASSKAYA, Olga V.
Serial No.:	11/183,232	Group Art Unit:	1615
Filed:	July 18, 2005	Confirmation No.	8078
Title:	DRUG-CONTAINING IMPLANTS AND METHODS OF USE THEREOF		

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

I, Steven SIEGEL, a citizen of United States of America, residing at 740 Heatherstone Drive, Berwyn, PA 19312, hereby declare:

1. I am an Associate Professor at the University of Pennsylvania. I have more than fourteen years of experience in Biomedical Science and Neurobiology. I received my MD and PhD in Neurobiology at the Mount Sinai School of Medicine in 1996 after completing an undergraduate degree in Neuroscience at Colgate University in 1986. I later completed residency in Psychiatry and a Fellowship in Neuropsychiatry at the University of Pennsylvania before joining the faculty in 2001. I am currently the Director of the Translational Neuroscience Program in Department of Psychiatry and the Director of the Clinical Neurosciences Track for the School of Medicine at Penn. I am also a practicing psychiatrist specializing in the treatment of Schizophrenia.

2. My fields of research expertise include designing and developing surgically implantable long-term delivery systems for the treatment of schizophrenia

and other major neuropsychiatry conditions. My laboratory develops and validates animal models of schizophrenia and autism to foster better understanding of the disorders and their treatments.

3. I have read the above-identified patent application, of which I am a named inventor, and have reviewed its prosecution history, including the Office Action of August 5, 2011. The subject application describes, *inter alia,* a biodegradable implant comprising a therapeutic drug and a polymer.

4. Claims 1, 8, 14, 21-23, 29, 35, 36, and 97 are pending in this application. These claims are directed to a biodegradable implant comprising a therapeutic drug and a polymer, said polymer comprising polylactic acid (PLA) and polyglycolic acid (PGA) in a PLA:PGA molar ratio between 50:50 and 100:0, wherein said therapeutic drug is present in an amount of 10%-60% of the mass of said implant, and said polymer is present in an amount of 40%-90% of the mass of said implant, wherein said therapeutic drug in said implant is capable of exhibiting the time to maximum concentration ranging from about 20 days to about 190 days, and wherein said therapeutic drug comprises risperidone, 9-OH-risperidone, or an active metabolite thereof.

5. The specification provides exemplifications of the claimed invention. Specifically, Examples show risperidone loading at concentrations more than 10%. *See* Examples 3, 4, 8, 10 and 13. It would be unreasonable to expect initial theoretical drug concentrations of 10% or more due to possible saturation and subsequent crystallization of the drug. Therefore, it was surprising that we could incorporate as much as 10-60% risperidone into the PLA:PGA copolymer, as claimed in the subject Application. Furthermore, in the subject Application, surprisingly and unexpectedly, the release of risperidone was achieved at the loading concentrations of 10%-60%. *See* Example 3, 4, 8, 10 and 13 of the Specification.

6. In the Office Action dated August 5, 2011, the Examiner rejected claims 1, 8, 14, 29, 35, 36, and 97 under 35 U.S.C. § 103, as allegedly being obvious over U.S. Patent Application Publication 2002/0179096 ("Siegel") in view of U.S.

Patent No. 5,871,778 ("Kino"). Specifically, the Examiner asserts that Siegel teaches a surgically implantable drug delivery device for long-term delivery of the antipsychotic drug and Kino teaches risperidone. Accordingly, the Examiner finds that it would have been obvious to combine the references to arrive at the invention.

7. I am the first-named inventor in the Siegel reference, discussed herein. The work described in the Siegel reference was conducted in my laboratory. I was the principal investigator for the work described in the Siegel reference.

8. Independent claim 1 recites "**therapeutic drug** is present in an amount of **10%-60% of the mass of said implant**, and said **polymer** is present in an amount **of 40%-90% of the mass of said implant**, wherein said therapeutic drug in said implant is capable of exhibiting the time to maximum concentration ranging from about **20 days** to about **190 days**...and wherein said therapeutic drug is **risperidone**." [emphasis added]. Nowhere does Siegel teach or suggest this combination of claimed features. Rather, Siegel relates to haloperidol loaded implant, not risperidone loaded implant as claimed. In particular, Siegel discusses implants comprising 20 to 40% haloperidol (at page 3, paragraph 23 and examples at pages 4 to 5 of Siegel), and thus Siegel's is directed to haloperidol implant, not risperidone implant as claimed.

9. Exhibits 1-3 that fully demonstrates that different drugs have different release rates in PLGA matrices. A type of drug plays a role in setting the release rate. *See* Exhibit 1 (Siegel *et al.*, *European J. Pharmaceutics and Biopharmaceutics*, 2006, vol. 64, pages 287-293); *See also* Exhibit 2 (Frank *et al., J. Control. Release*, 2005, vol. 102, pages 333-334, published online on November 14, 2004); *See also* Exhibit 3 (Kiortosis *et al., European J. Pharmaceutics and Biopharmaceutics*, 2005, vol. 59, pages 73-83, published online on July 2, 2004). For example, Table 1 in Exhibit 1 shows no correlation between drug types and release rates in PLGA matrices. Accordingly, different drugs release at different rates from PLGA matrices, and thus to infer from one drug the effects in another is misleading. Therefore, one could not expect or predict the release rate of risperidone as claimed, based on Siegel's haloperidol.

10. In addition, it is well known that these are different drugs having different chemical and physical properties. Because of the existence of chemical polymorphisms, one could not expect whether the arrangement and/or conformation of molecules in the crystal lattice would change or not while combining the drug and the polymer during solvent casting or other approaches to form an implant.

11. Kino does not cure the defect in Siegel. Specifically, Kino relates only to bromperidol or haloperidol loaded into dl-Polylactic acid or Poly(lactic-co-glycolic) acid (50:50) for making a microcapsule, which is not an implant as claimed. Although Kino describes a laundry list of active materials including risperidone, it provides no data or support for how much of each active ingredient that can be loaded in to each biodegradable polymer.

12. For the sake of arguments, even if a person is motivated to try risperidone, he or she could not expect or predict that risperidone at concentrations of 10% or more would be effective with the claimed PLGA polymer. With PLGA polymer, the incorporation efficiency decreases with increasing drug concentration. *See* Exhibit 4 (Budhian *et al.*, 2005, *J. of Microencapsulation*, vol. 22(7), pages 773-785). Studies have shown that the final drug content in PLGA polymer has an upper limit, which cannot be increased simply by increasing the initial drug concentration. *See Id.* at 778; *See also* Exhibit 5 (Chorny *et al.*, 2002, *J. of Controlled Release*, vol. 83, pages 401-414); *See also* Exhibit 6 (Baichello *et al.*, 1999, *Drug Development and Industrial Pharmacy*, vol. 25, pages 471-476). Any such increase in the initial drug concentration would result in burst release of the drug or crystallization of the drug.

13. For instance, at higher drug loading concentrations, an initial burst of drug release was observed with PLGA microparticles. *See* Exhibit 7 (Choi *et al*, 2001, *Bull. Korean Chem. Soc.*, vol. 32, pages 867-872). Specifically, at 20% initial drug loading concentration, PLGA particles released 56% of encapsulated drug in 2 hours. *Id.* at 870-871. Accordingly, the high initial drug

concentrations in PLGA results in quick burst release, not long term release as claimed.

14. Additionally, at the maximum, only 2% of drug could be loaded into PLGA polymer system. Any increase in drug concentration beyond 2.5 mg/ml caused the drug content to decrease because the drug molecules within the polymer matrix are attracted towards the drug molecules in the aqueous phase and migrate to aqueous phase and nucleate drug crystals. *See* Exhibit 8 (Budhian *et al.*, 2007, *Intl. J. of Pharmaceutics*, vol. 336, pages 367-375). As a result, the high initial drug concentrations results in crystallization of drug. *Id.* at 372.

15. Therefore, an attempt to incorporate as much as 10-60% risperidone into the PLA:PGA copolymer to provide the release rate of time to maximum concentration 20-190 days, as claimed, in the subject Application cannot be expected in view of the cited references or any other reference in the art.

I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements, and the like so made, may jeopardize the validity of the application or any patent issuing thereon.

Date: December 05, 2011

Dr. Steven Siegel